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(54) Title: PROCESS TO BETA-KETOAMIDE INTERMEDIATES TO DIPEPTIDYL PEPTIDASE INHIBITORS

(57) Abstract: A novel process is provided for the preparation of beta-ketoamide intermediates which are useful in the synthesis of dipeptidyl peptidase-IV inhibitors for the treatment of type 2 diabetes. Also provided are useful intermediates obtained from the process.

TITLE OF THE INVENTION

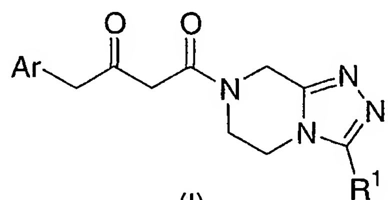
PROCESS TO BETA-KETOAMIDE INTERMEDIATES TO DIPEPTIDYL PEPTIDASE INHIBITORS

FIELD OF THE INVENTION

The present invention discloses a novel process and novel intermediates toward the preparation of beta-ketoamide intermediates which are useful in the synthesis of dipeptidyl peptidase-IV (DP-IV) inhibitors for the treatment of type 2 diabetes.

BACKGROUND OF THE INVENTION

The present invention provides a process for the preparation of beta-ketoamides of structural formula I:



(I)

wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines.

The present invention also provides structurally novel intermediates useful in the disclosed process and in the preparation of DP-IV inhibitors.

In the present invention, compounds of structural formula I are produced in an efficient manner in two chemical steps starting with an appropriately substituted phenylacetic acid and Meldrum's acid.

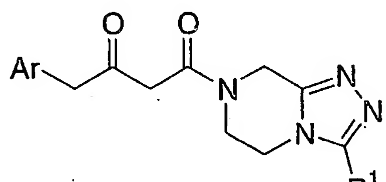
SUMMARY OF THE INVENTION

This invention is concerned with a process for preparing substituted beta-ketoamides of structural formula I and certain useful intermediates obtained during that process. The process involves the reaction of an activated optionally substituted phenylacetic acid with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) to generate an intermediate Meldrum's acid adduct which is then reacted with an optionally substituted 5,6,7,8-tetrahydro[1,2,4]-triazol[4,3-*a*]pyrazine to afford the desired product.

Compounds of structural formula I represent key intermediates in the synthesis of dipeptidyl peptidase-IV (DP-IV) inhibitors disclosed in WO 03/004498 (published 16 January 2003) which are useful for the treatment of type 2 diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention involves the preparation of a compound of structural formula I:



(I)

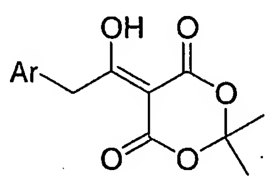
wherein

Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and

R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;

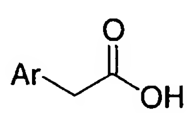
comprising the steps of:

(a) producing a compound of structural formula II:



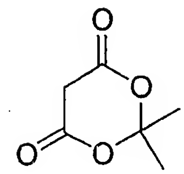
(II)

by treating a phenylacetic acid of structural formula III:



(III)

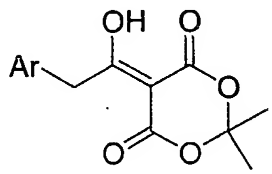
with an acid activating reagent and 2,2-dimethyl-1,3-dioxane-4,6-dione of structural formula IV:



(IV)

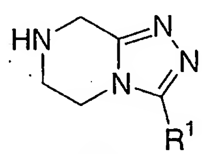
in a suitable organic solvent; and

(b) treating a compound of structural formula II:



(II)

with a 5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-*a*]pyrazine of structural formula V:



(V)

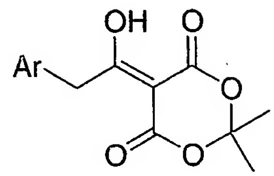
or an acid salt thereof,

in the presence of acid or base in a suitable organic solvent to afford a compound of structural formula I.

In one embodiment of the process of the present invention, R^1 is CF_3 and Ar is phenyl substituted with one to three substituents independently selected from the group consisting of fluorine, bromine, and trifluoromethyl. In a class of this embodiment Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

In another embodiment of the process of the present invention, the final product of the reaction sequence of structural formula I is isolated from the reaction mixture. In a further embodiment, the final product can be used without isolation for further chemical modification into later-stage compounds.

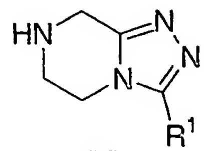
The first step in the process of the present invention entails the preparation of a Meldrum's acid adduct of structural formula II:



(II)

This is accomplished by treating an appropriately substituted phenylacetic acid with a carboxyl group activating agent to generate an active carboxylic acid species, such as an acyl halide; an active ester, such as an aryl ester; a mixed carboxylic acid anhydride; an acyl imidazole; a mixed carboxylic acid carbonic acid anhydride; and a phosphoric or phosphinic acid mixed anhydride. The activated phenylacetic acid is allowed to react with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in the presence of base. Formation of the active carboxylic acid species is carried out using methods that are well-known in the practice of organic chemistry. For example, 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole may be used to generate an acyl imidazole; trimethylacetyl (pivaloyl) chloride or isovaleryl chloride to generate a pivalic or isovaleric acid mixed anhydride; oxalyl chloride (in the presence of a catalytic amount of DMF) or phosphorus pentachloride to generate an acid chloride; isobutyl chloroformate to generate an isobutylcarbonic acid mixed anhydride; and diethylcyanophosphate or diethylchlorophosphate to generate a diethylphosphoric acid mixed anhydride. Examples of active aryl esters include *p*-nitrophenyl esters, 2,4-dinitrophenyl esters, and pentafluorophenyl esters. Meldrum's acid may be initially present in the reaction mixture during the formation of the activated acid species or added subsequently after generation of the activated acid species. The reaction is carried out in a suitable organic solvent, such as THF, dimethoxymethane, DME, DMF, DMAc, NMP, DMSO, IPAc, EtOAc, MTBE, toluene, and MeCN. If formation of the activated acid species liberates acid, then the reaction is carried out in the presence of base, such as triethylamine, *N,N*-diisopropylethylamine, diisopropylamine, 2,4,6-collidine, imidazole, pyridine, lutidine, *N,N*-dimethylaniline, DMAP, DABCO, and DBU. In one embodiment the Meldrum's acid adduct is prepared using the combination of pivaloyl chloride and DMAP.

The subsequent and final step in the process of the present invention entails reaction of the Meldrum's acid adduct of structural formula II with a 5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-*a*]pyrazine of structural formula V:



(V)

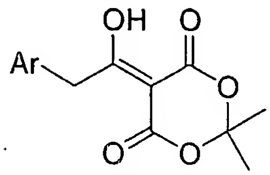
or an acid salt thereof. When an acid salt of the triazole species is used, a base or an acid can be added to the reaction mixture. Embodiments of bases that can be used in this reaction include triethylamine, *N,N*-diisopropylethylamine, diisopropylamine, 2,4,6-collidine, imidazole, pyridine, lutidine, DMAP, DABCO, and DBU. Embodiments of acids that can be used in this reaction include trifluoroacetic acid, trichloroacetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, camphorsulfonic acid, acetic acid, and pivalic acid. A preferred acid is trifluoroacetic acid. The reaction is carried out in a suitable reaction solvent, such as THF, dimethoxymethane, DME, EtOAc, IPAc, MeCN, DMF, DMAc, NMP, DMSO, MTBE, and toluene.

In one embodiment of the present process the ketoamide formation is carried out in acidic reaction media to achieve high conversion and high yield. Otherwise, the accuracy of the base charge in the formation of the Meldrum's acid adduct is critical in order to ensure that the ketoamide formation step proceeds in high yield and conversion. Introducing an acid into the reaction system is advantageous, in that it neutralizes the excess base used in formation of the Meldrum's acid adduct if a through-process is applied and results in high conversion allowing for lowering the reaction temperature and suppressing formation of impurities.

In one embodiment, the Meldrum's acid adduct is not isolated from the reaction mixture but is reacted with a triazole species of formula V, preferably in the form of an acid salt, such as the hydrochloride salt. The reaction is carried out optionally in the presence of acid in a suitable organic solvent. This embodiment is referred to as a "through-process."

The compound of structural formula I need not be isolated, but can be further modified to obtain the DP-IV inhibitors disclosed in WO 03/004498.

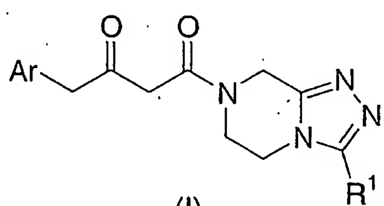
A further embodiment of the present invention comprises the following novel compounds of structural formula II which are intermediates in the preparation of the compounds of structural formula I:



(II)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy. In one embodiment of the novel intermediates of structural formula II, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

Yet a further embodiment of this invention comprises the following novel compounds of structural formula I which are useful intermediates in the preparation of the dipeptidyl peptidase (DP-IV) inhibitors disclosed in WO 03/004498:



(I)

wherein

Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines.

In one embodiment of the novel intermediates of structural formula I, Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^1 is trifluoromethyl.

Representative experimental procedures utilizing the novel process are detailed below. For purposes of illustration, the following Examples are directed to the preparation of beta-ketoamide 2-3, but doing so are not intended to limit the process of the present invention to the specific conditions for making this particular compound.

Abbreviations: DABCO is 1,4-diazabicyclo[2.2.2]octane; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAc is *N,N*-dimethylacetamide; DMAP is 4-(dimethylamino)pyridine; DME is 1,2-dimethoxyethane; DMF is *N,N*-dimethylformamide; DMSO is dimethylsulfoxide; EtOAc is ethyl acetate; EtOH is ethanol; HPLC is high-performance liquid chromatography; IPAc is isopropyl acetate; MeCN is acetonitrile; MeOH is

methanol; MTBE is methyl *t*-butyl ether; NMP is N-methylpyrrolidinone; and THF is tetrahydrofuran.

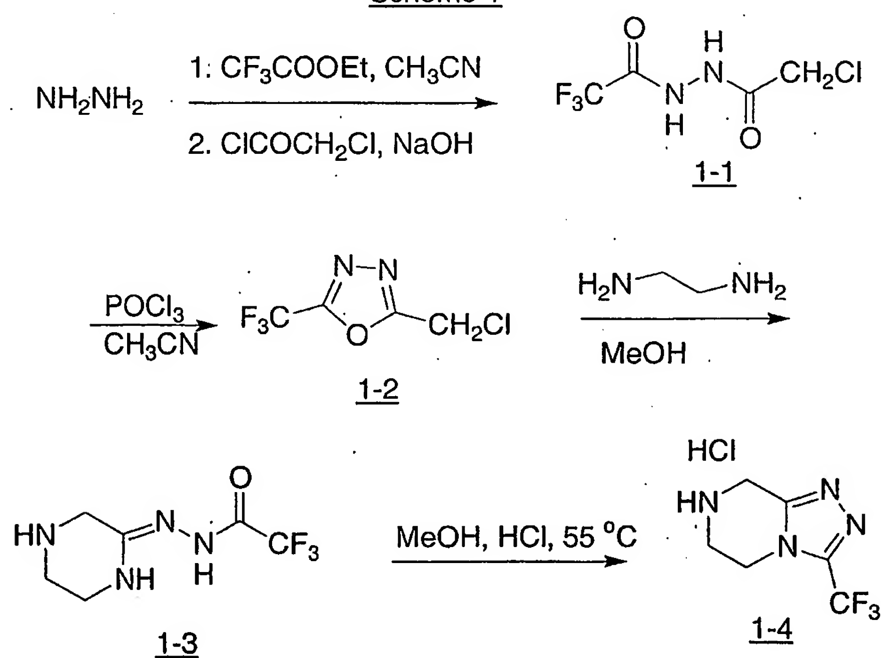
By halogen is meant fluorine, chlorine, bromine, or iodine.

The starting materials are either commercially available or known in the chemical scientific or patent literature. Purification procedures include e.g., distillation, crystallization and normal or reverse phase liquid chromatography.

EXAMPLES 1-6

I. Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

Scheme 1



Step A: Preparation of bishydrazide (1-1)

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to

remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume (approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole (1-2)

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC).

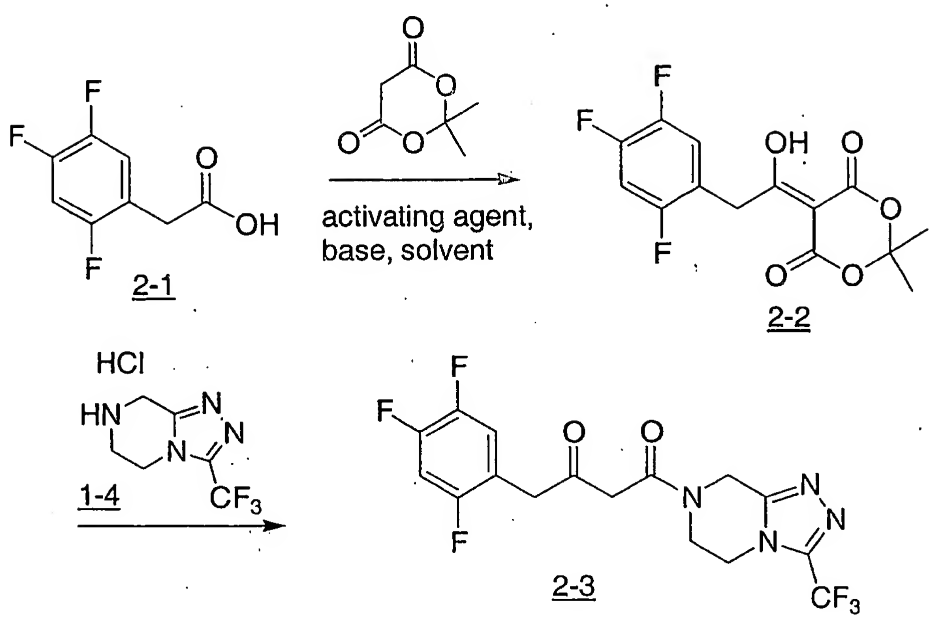
^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.9 (t, 2H), 3.2 (t, 2H), 3.6 (s, 2H), and 8.3 (b, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-d_6): δ 40.8, 42.0, 43.3, 119.3 (q, J = 350 Hz), 154.2, and 156.2 (q, J = 38 Hz) ppm.

Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50 mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC).
^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ: 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

II. Preparation of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-one (2-3)

Scheme 2



Example 1: Use of Acetonitrile as Solvent and Pivaloyl Chloride as Acid Activating Agent

2,4,5-Trifluorophenylacetic acid (2-1) (available from several commercial suppliers) (0.25 kg, 1.32 mol), Meldrum's acid (0.21 kg, 1.45 mol), and DMAP (12.9 g, 0.11 mol) were charged into a 5 L three-neck flask. Acetonitrile (750 mL) was added in one portion at room temperature. *N,N*-diisopropylethylamine (492 mL, 2.83 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (178 mL, 1.45 mol) was added dropwise over 1 to 2 h while maintaining the temperature below 50 °C. The reaction was aged at 45-50 °C for 2-3 h. Triazole hydrochloride 1-4 (0.30 kg, 1.32 mol) was added in one portion at 40-50 °C. Trifluoroacetic acid (30.3 mL, 0.39 mol) was added dropwise, and the reaction solution aged at 50-55 °C for 6 h. Without further work-up, the crude reaction mixture containing 2-3 can be used directly for conversion into DP-IV inhibitors. The isolated solution yield was 88-90%.

Example 2: Use of DMAc as Solvent and Pivaloyl Chloride as Acid Activating Agent

2,4,5-Trifluorophenylacetic acid (2-1) (150 g, 0.789 mol), Meldrum's acid (125 g, 0.868 mol), and DMAP (7.7 g, 0063 mol) were charged into a 5 L three-neck flask. DMAc (525 mL) was added in one portion at room temperature. *N,N*-diisopropylethylamine (282 mL, 1.62 mol) was added in one portion at room temperature while maintaining the temperature below 40

°C. Pivaloyl chloride (107 mL, 0.868 mol) was added dropwise over 1 to 2 h while maintaining the temperature below 50 °C. The reaction mixture was aged at 45-50 °C for 2-3 h. Triazole hydrochloride 1-4 (180 g, 0.789 mol) was added in one portion at 40-50 °C. The reaction solution was aged at 70 °C for several h. 5% Aqueous sodium hydrogencarbonate solution (625 mL) was then added dropwise at 20 – 45 °C. The batch was seeded and aged at 20 – 30 °C for 1-2 h. Then an additional 525 mL of 5% aqueous sodium hydrogencarbonate solution was added dropwise over 2-3 h. After aging several h at room temperature, the slurry was further cooled to 0 – 5 °C and aged 1 h before filtering the solid. The wet cake was displacement-washed with 20% aqueous DMAc (300 mL), followed by an additional two batches of 20% aqueous DMAc (400 mL), and finally water (400 mL). The cake was suction-dried at room temperature. The isolated yield of final product was 89%.

In CD_3CN solution, 2-3 exists as a 4:3 mixture of amide rotamers (hindered rotation around the Nitrogen-Carbonyl bond). Severe overlap of signals does not permit unequivocal assignment of each rotamer. Assignments are grouped (when necessary) and rotamers (major/minor/both) denoted. Complexity due to ^{19}F spin-spin coupling does not permit assignment of all ^{13}C resonances, therefore, select ^{13}C data are presented. The structure shown is the major rotamer in solution.

^1H NMR (400 MHz, CD_3CN): δ 7.23-7.07 (overlapping m, 2H, both), 4.91 (s, 2H, major), 4.81 (s, 2H, minor), 4.16 (t, J = 5.6 Hz, 2H, major), 4.11 (t, J = 5.6 Hz, 2H, minor), 4.00 (t, J = 5.6 Hz, 2H, minor), 3.92 (s, 2H, major), 3.91 (s, 2H, minor), 3.83 (t, J = 5.6 Hz, 2H, major), 3.80 (s, 2H, major), 3.78 (s, 2H, minor) ppm; ^{13}C NMR (100 MHz, CD_3CN, selected data): δ 201.43 (both), 167.37 (minor), 167.27 (major), 151.88 (major), 151.53 (minor), 48.88 (minor), 48.81 (major), 44.65 (major), 44.19 (minor), 43.86 (minor), 43.08 (major), 43.00 (both), 39.82 (major), 38.81 (minor) ppm.

Example 3: Use of Acetonitrile as Solvent and Pivaloyl Chloride as Acid Activating Agent

2,4,5-Trifluorophenylacetic acid (2-1) (available from several commercial suppliers) (25 g, 0.132 mol), Meldrum's acid (21 g, 0.145 mol), and DMAP (1.29 g, 0.011 mol) were charged into a 1000 mL three-neck flask. Acetonitrile (75 mL) was added in one portion at room temperature. *N,N*-diisopropylethylamine (49.2 mL, 0.283 mol) was added in one portion at room temperature while maintaining the temperature below 40 °C. Pivaloyl chloride (17.8 mL, 0.145 mol) was added dropwise over 1 to 2 h while maintaining the temperature below 50 °C. The reaction was aged at 45-50 °C for 2-3 h and cooled to 0 °C. 1*N* HCl (300 mL) was added dropwise over 1 h while the Meldrum's adduct 2-2 was crystallized out. The product was

collected by filtration and washed twice with 20% MeCN/water. After drying, 36.5 g of the Meldrum's acid adduct was obtained (88% yield):

^{1}H-NMR (400 MHz, $CDCl_3$): δ 15.50 (s, 1H), 7.14 (m, 1H), 6.96 (m, 1H), 4.45 (s (2 H), 1.76 (s, 6 H)ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.76, 170.66, 160.42, 156.47 (ddd, J_{CF} = 245.7, 9.6, 2.4 Hz), 149.79 (ddd, J_{CF} = 251.4, 14.5, 12.0 Hz), 146.90 (ddd, J_{CF} = 244.9, 12.0, 3.2 Hz), 119.40 (dd, J_{CF} = 19.3, 5.6 Hz), 117.41 (ddd, J_{CF} = 18.5, 5.6, 4.0 Hz), 105.80 (dd, J_{CF} = 28.1, 20.9 Hz),

105.63, 91.99, 34.59, 27.06 ppm.

Example 4: Use of CDI as Acid Activating Agent

2,4,5-Trifluorophenylacetic acid (2-1) (11.4 g, 60 mmol) was dissolved in THF (60 mL) and 1,1'-carbonyldiimidazole (10.7 g, 66 mmol) was added over 5 min. The mixture was warmed to 51 °C, Meldrum's acid (9.51 g, 66 mmol) was added, and the mixture was aged for 3 h.. The reaction mixture was diluted with IPAc (60 mL) and water (60 mL), and the pH was adjusted to 2.4 with concentrated hydrochloric acid (11.5 mL). The aqueous layer was separated, and the organic layer was washed at 36 °C with 0.1 N HCl (60 mL). The organic layer was concentrated, flushed with IPAc, and the residue was slurried in 2:1 heptane/IPAc (70 mL). The mixture was cooled over an ice-bath, then filtered, rinsing the solids with 2:1 heptane/IPAc. After drying, the Meldrum's acid adduct was obtained as a solid (15.1 g) in 80% yield.

The Meldrum's acid adduct (22.1 g, 70 mmol) and the triazole hydrochloride 1-4 (16.0 g, 70 mmol) were slurried in IPAc (220 mL) and *N,N*-diisopropylethylamine (12.8 mL) was added. After aging for 3.5 h at 85 °C, water (175 mL) was added and the mixture was transferred to a separatory funnel with a 40-mL rinse with IPAc. The aqueous layer was separated and the organic layer was washed with water (100 mL). The organic layer was partially concentrated under reduced pressure to give a 65 g of solution of the ketoamide 2-3 in IPAc. *n*-Heptane (30 mL) was added at room temperature, followed by seed crystals of ketoamide. Additional heptane (20 mL) was added dropwise, and the mixture was stirred overnight. Additional heptane (50 mL) was added slowly and after aging for 2 h, the solids were filtered and washed with 2.2:1 heptane/IPAc (30 mL). After drying, the ketoamide 2-3 was obtained in 92% yield (26.3 g).

Example 5: Through-process for the preparation of ketoamide 2-3 in DMAc

To 25 mL of DMAc was added the trifluorophenylacetic acid (5 g), CDI (4.3 g), and the resulting mixture was heated to 45 °C for 10 min. The reaction was allowed to cool to

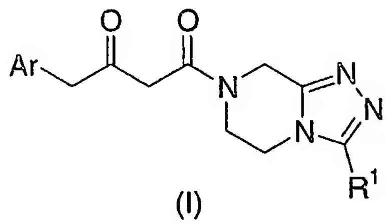
20 °C and degassed. Meldrum's acid (4.2 g) was added and the mixture was aged 24 h at 20 °C, and then 1 h at 50 °C. The triazole hydrochloride 1-4 (6 g) was added and the reaction mixture was stirred for 12 h at 90 °C. The reaction mixture was cooled to 50 °C and water (40 mL) was added crystallizing the product. The slurry was cooled to 20 °C and stirred for 12 h and water (35 mL) was added over 3 h. After 2 h, the solid was isolated by filtration and dried to give 7.4 g of 2-3 (69% yield).

Example 6: Through-process for the preparation of ketoamide 2-3 in IPAc

To 45 mL of IPAc was added the trifluorophenylacetic acid (5 g), CDI (4.3 g), and the resulting mixture was heated to 45 °C for 10 min. The reaction was allowed to cool to 20 °C and degassed. Meldrum's acid (4.2 g) was added and the mixture was aged 24 h at 20 °C, and then 1.5 h at 40 °C. The triazole hydrochloride 1-4 (6 g) was added and the reaction mixture was stirred for 12 h at 90 °C. The reaction mixture was cooled to 20 °C and the mixture was washed with water (2 x 50 mL). The solution contained 7.8 g of the product 2-3 (74% yield).

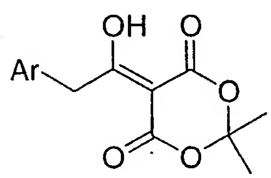
WHAT IS CLAIMED IS:

1. A process for preparing a compound of structural formula I:



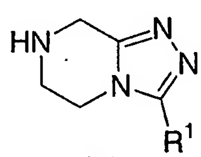
(I)

wherein
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;
comprising the step of treating a compound of structural formula II:



(II)

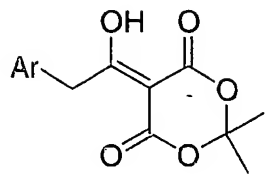
wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy;
with a 5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-*a*]pyrazine of structural formula V:



(V)

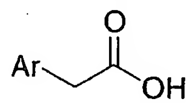
or an acid salt thereof in the presence of acid or base in a suitable organic solvent.

2. The process of Claim 1 additionally comprising the step of producing a compound of structural formula II:



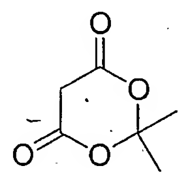
(II)

by treating a phenylacetic acid of structural formula III:



(III)

with an acid activating agent and 2,2-dimethyl-1,3-dioxane-4,6-dione of structural formula IV:



(IV)

in a suitable organic solvent.

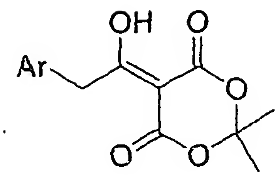
3. The process of Claim 1 wherein R^1 is trifluoromethyl and Ar is phenyl substituted with one to three substituents independently selected from the group consisting of fluorine, bromine, and trifluoromethyl.

4. The process of Claim 3 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

5. The process of Claim 2 wherein said acid activating agent is pivaloyl chloride or 1,1'-carbonyldiimidazole.

6. The process of Claim 1 wherein said acid is trifluoroacetic acid.

7. A compound of structural formula II:

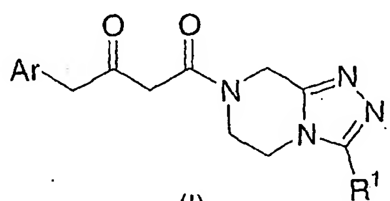


(II)

wherein Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy.

8. The compound of Claim 7 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl.

9. A compound of structural formula I:

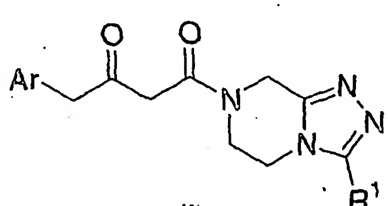


(I)

wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines.

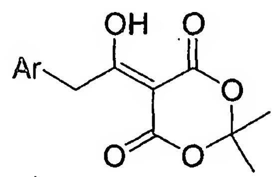
10. The compound of Claim 9 wherein Ar is 2,5-difluorophenyl or 2,4,5-trifluorophenyl and R^1 is trifluoromethyl.

11. A process for preparing a compound of structural formula I:



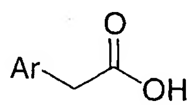
(I)

wherein
Ar is phenyl which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, trifluoromethyl, and trifluoromethoxy; and
R^1 is hydrogen or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines;
comprising the steps of:
(a) producing a compound of structural formula II:



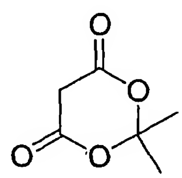
(II)

by treating a phenylacetic acid of structural formula III:



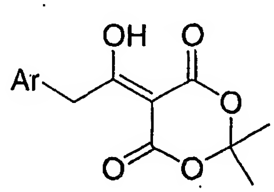
(III)

with an acid activating reagent and 2,2-dimethyl-1,3-dioxane-4,6-dione of structural formula IV:



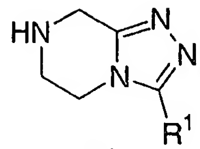
(IV)

in a suitable organic solvent; and
(b) treating a compound of structural formula II:



(II)

with a 5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-*a*]pyrazine of structural formula V:



(V)

or an acid salt thereof,

in the presence of acid or base in a suitable organic solvent to afford a compound of structural formula I.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/007834

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 C07D319/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/004498 A (EDMONDSON SCOTT D ; KIM DOOSEOP (US); PARMEE EMMA R (US); WEBER ANN E) 16 January 2003 (2003-01-16) cited in the application Page 24, line 16, to page 28, line 14.	1-11
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002289950 Database Accession No. 4688512 (BRN). & SYNTHESIS, vol. 12, 1992, pages 1213-1214,	7
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002289951 Database Accession No. 8268720 (BRN). -/--	7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2004	11/08/2004

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& J. ORG. CHEM., vol. 64, no. 8, 1999, pages 2814-2820, -----	
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002289952 Database Accession Nos. 3552873, 9131622, 9132048, 9132318, 9133751, 9133870, 9140551 (BRNs). & BIOORG. MED. CHEM. LETT., vol. 12, no. 8, 2002, pages 1153-1158, -----	7
P,X	MALAKHOV, A. D. ET AL.: "1-(Phenylethynyl)pyrene and 9,10-bis(phenylethynyl)anthracene, useful fluorescent dyes for DNA labeling: excimer formation and energy transfer" EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, no. 6, 3 March 2004 (2004-03-03), pages 1298-1307, XP002289949 Page 1299, compound 4. -----	7

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US2004/007834

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03004498 A	16-01-2003	BR 0210866 A	29-06-2004
		CA 2450740 A1	16-01-2003
		EP 1412357 A1	28-04-2004
		HR 20031098 A2	30-06-2004
		NZ 529833 A	19-12-2003
		WO 03004498 A1	16-01-2003
		US 2003100563 A1	29-05-2003